WHAT IS CLAIMED IS:

1. An oligonucleotide comprising a sequence of nucleotide units capable of specifically hybridizing to a strand of nucleic acid, wherein:

at least one of said nucleotide units is functionalized to increase nuclease resistance of said oligonucleotide;

at least one of said nucleotide units bears a substituent group that increases binding affinity of said oligonucleotide to said strand of nucleic acid; and

a plurality of said nucleotide units have 2′-deoxy-erythro-pentofuranosyl sugar moieties, said 2′-deoxy-erythro-pentofuranosyl nucleotide units being consecutively located in said sequence of nucleotide units.

2. The oligonucleotide of claim 1 wherein said substituent group for increasing binding affinity comprises a 2′-substituent group.

3. The oligonucleotide of claim 2 wherein said 2′-substituent group is fluoro, C1-C9 alkoxy, C1-C9 aminoalkoxy, allyloxy, imidazolealkoxy and poly(ethylene glycol).

4. The oligonucleotide of claim 1 wherein each of said nucleotide units is a phosphorothioate or phosphorodithioate nucleotide.

5. The oligonucleotide of claim 1 wherein the 3′ terminal nucleotide unit of said oligonucleotide includes a nuclease resistance modifying group on at least one of the 2′ or the 3′ positions of said nucleotide unit.

6. The oligonucleotide of claim 1 wherein:

a plurality of said nucleotide units bear substituent groups that increases binding affinity of said oligonucleotid to said strand of nucleic acid, said substituent-bearing nucleotides being divided into a first nucleotide unit sub-sequence and a second nucleotide unit sub-sequence; and

said plurality of 2′-deoxy-erythro-pentofuranosyl nucleotide units is positioned in said sequence of nucleotide units between said first nucleotide unit sub-sequence and said second nucleotide unit sub-sequence.

7. The oligonucleotide of claim 1 wherein:

a plurality f said nucleotide units bear substituent groups that increase binding affinity of said ligonucleotide to said complementary strand of nucleic acid; and

at least a portion of said substituent-bearing nucleotide are consecutively located at one of the 3′ terminus or the 5′ terminus of said oligonucleotide.

8. The oligonucleotide of claim 1 wherein at least five of said nucleotide units have 2′-deoxy-erythro-pentofuranosyl sugar moieties, said at least five 2′-deoxy-erythro-pentofuranosyl nucleotide units being consecutively located in said sequence of nucleotide units.

9. The oligonucleotide of claim 1 wherein from ne to about eight of said nucleotide units bear a substituent group that increases the binding affinity of said oligonucleotide to said complementary strand, said substituent-bearing nucleotide units being consecutively located in said sequence of nucleotide units.

10. The oligonucleotide of claim 1 wherein:

from one to about eight of said nucleotide units bear a substituent group for increasing the binding affinity of said oligonucleotide to said complementary strand, said substituent-bearing nucleotide units being consecutively located in said sequence of nucleotide units; and

at least five of said nucleotide units have 2′-deoxy-erythro-pentofuranosyl sugar moieties, said at least five 2′-deoxy-erythro-pentofuranosyl nucleotide units being consecutively located in said sequence of nucleotide units.

11. An oligonucleotide comprising a sequence f phosphorothioate nucleotides capable of specifically hybridizing to a strand of nucleic acid, wherein:

a plurality of said nucleotides bear a substituent group that increases binding affinity of said oligonucleotide to said strand of nucleic acid; and

a plurality of said nucleotides have 2′-deoxy-erythro-pent furanosyl sugar moi ties.

12. Th oligonucleotide of claim 11 wher in said substituent group for incr asing binding affinity compris s a

2′-substituent gr up.

13. The oligonucleotide of claim 12 wherein said 2′-substituent group is fluoro, C1-C9 alkoxy, C1-C9 aminoalkoxy r allyloxy.

14. The oligonucleotide of claim 12 including: a further plurality of said nucleotides bearing 2′-substituent groups;

said 2′-deoxy-erythro-pentofuranosyl nucleotides being positioned in said oligonucleotide between groups of nucleotides having said 2′-substituent group located thereon.

15. The oligonucleotide of claim 11 wherein said substituent-bearing nucleotides are located at one of the 3′ terminus or the 5′ terminus of said oligonucleotide.

16. An oligonucleotide comprising a sequence of phosphorothioate nucleotides capable of specifically hybridizing to a strand of nucleic acid, wherein:

a first portion of said nucleotides have 2′-deoxy-2′-fluoro, 2′-methoxy, 2′-ethoxy, 2′-propoxy, 2′-aminopropoxy or 2′-allyloxy pentofuranosyl sugar moieties; and

a further portion of said nucleotides have 2′-deoxy-erythro-pentofuranosyl sugar moieties.

17. An oligonucleotide of claim 16 wherein said first portion of said nucleotides are located at either the 3′ terminus or the 5′ terminus of said oligonucleotide.

18. An oligonucleotide of claim 17 including:

an additional portion of said nucleotides having 2′-d oxy-2′-fluoro, 2′-methoxy, 2′-ethoxy, 2′-propoxy, 2′-aminopropoxy or 2′-allyloxy pentofuranosyl sugar moieties; and

said further portion of said nucleotides positioned in said oligonucleotide between said first portion of nucleotides and said additional portion of said nucleotides.

19. A method of treating an organism having a diseas characterized by the undesired production of a protein comprising contacting the organism with an oligonucleotide having a s quence of nucleotides capable of specifically hybridizing to a strand of nucleic acid coding f r said pr tein at least one of th nucl otides being functi nalized to

increase nuclease resistance of the oligonucleotide, a plurality of the nucl otides having a substituent group located thereon to increase binding affinity of the oligonucleotide to the strand of nucleic acid, and a plurality of the nucleotides having 2′-deoxy-erythro-pentofuranosyl sugar moieties.

20. The method of claim 19 wherein each of said nucleotides is a phosphorothioate nucleotide.

21. The method of claim 19 wherein said substituent group is a 2′-substituent group.

22. The method of claim 21 wherein said 2′-substituent group is fluoro, alkoxy, aminoalkoxy or allyloxy.

23. A pharmaceutical composition comprising:

an pharmaceutically effective amount of an oligonucleotide having a sequence of nucleotides capable of specifically hybridizing to a strand of nucleic acid, at least one of the nucleotides being functionalized to increase nuclease resistance of the oligonucleotide, a plurality of the nucleotides having a substituent group located thereon to increase binding affinity of the oligonucleotide to a complementary strand of nucleic acid; a plurality of the nucleotides having 2′-deoxy-erythro-pentofuranosyl sugar moieties; and

a pharmaceutically acceptable diluent or carrier.

24. A method of modifying *in vitro* a sequence-specific nucleic acid, comprising contacting a test solution containing RNase H and said nucleic acid with an oligonucleotide having a sequence of nucleotides capable of specifically hybridizing to a strand of nucleic acid where at least one of the nucleotides is functionalized to increase nuclease resistance of the oligonucleotide, where a plurality of the nucleotides have a substituent group located thereon to increase binding affinity of the oligonucleotide to a complementary strand of nucleic acid, and where a plurality of the nucleotides have 2′-deoxy-erythro-pentofuranosyl sugar moieti s.

25. A method f c ncurrently enhancing hybridizati n and RNase H activation in a rganism comprising c ntacting the

organism with an olig nucleotide having a sequence of nucleotides capabl of specifically hybridizing to a complementary strand of nucleic acid and where at least one of the nucleotides is functionalized to increase nuclease resistance of the oligonucleotide, where a plurality of the nucleotides have a substituent group located thereon to increase binding affinity of the oligonucleotide to a complementary strand f nucleic acid, and where a plurality of the nucleotides have 2′-deoxy-erythro-pentofuranosyl sugar moieties.

26. A macromolecule comprising a plurality of nucleosides linked by covalent linkages in a sequence that is hybridizable to a complementary nucleic acid, wherein:

said nucleosides are selected from α-nucleosides, β-nucleosides including 2′-deoxy-erythro-pentofuranosyl β-nucleosides, 4′-thionucleosides and carbocyclic-nucleosides;

said linkages are selected from charged phosphorous linkages, neutral phosphorous linkages or non-phosphorous linkages; and

said sequence of linked nucleosides contains at least two nucleoside regions, wherein:

a first of said regions includes nucleosides selected from said α-nucleosides linked by charged and neutral 3′-5′ phosphorous linkages, said α-nucleosides linked by charged and neutral 2′-5′ phosphorous linkages, said α-nucleosides linked by non-phosphorous linkages, said 4′-thionucleosides linked by charged and neutral 3′-5′ phosphorous linkages, said 4′-thionucleosides linked by charged and neutral 2′-5′ phosphorous linkages, said 4′-thionucleosides linked by non-phosphorous linkages, said carbocyclic-nucleosides linked by charged and neutral 3′-5′ phosphorous linkages, said carbocyclic-nucleosides linked by charged and neutral 2′-5′ phosphorous linkages, said carbocyclic-nucleosides linked by non-phosphorous linkages, said β-nucleosides linked by charged and neutral 2′-5′ linkages, and said β-nucleosides linked by n n-

phosphor us linkages; and

a second of said regions consists of said 2'-deoxy-erythro-pentofuranosyl ß-nucleosides linked by charged 3'-5' phosphorous linkages having a negative charge at physiological pH.

27. A macromolecule of claim 26 wherein said sec nd region includes at least 3 of said 2'-deoxy-erythro-pentofuranosyl ß-nucleosides.

28. A macromolecule of claim 26 wherein said second nucleoside region is position between said first nucleoside region and a third nucleoside region, said third nucleosid region including nucleosides selected from said α-nucleosides linked by charged and neutral 3'-5' phosphorous linkages, said α-nucleosides linked by charged and neutral 2'-5' phosphorous linkages, said α-nucleosides linked by non-phosphorous linkages, said 4'-thionucleosides linked by charged and neutral 3'-5' phosphorous linkages, said 4'-thionucleosides linked by charged and neutral 2'-5' phosphorous linkages, said 4'-thionucleosides linked by non-phosphorous linkages, said carbocyclic-nucleosides linked by charged and neutral 3'-5' phosphorous linkages, said carbocyclic-nucleosides linked by charged and neutral 2'-5' phosphorous linkages, said carbocyclic-nucleosides linked by non-phosphorous linkages, said ß-nucleosides linked by charged and neutral 2'-5' linkages, and said ß-nucleosides linked by non-phosphorous linkages.

29. A macromolecule of claim 26 wherein said charged phosphorous linkages include phosphodiester, phosphorothioate, phosphorodithioate, phosphoroselenate or phosphorodiselenate linkages.

30. A macromolecule of claim 26 wherein said charged phosphorous linkages is phosphodiester or phosphorothioat .

31. A macromolecule of claim 26 wherein said neutral phosphorous linkages include alkyl and aryl phosphonates, alkyl and aryl phosphoroamidit s, alkyl and aryl phosphotriesters, hydrogen phosphonate and boranophosphate linkages.

32. A macromolecule of claim 26 wher in said non-

phosphorous linkages include peptide linkages, hydrazine linkages, hydroxy-amine linkages, carbamate linkages, morpholine linkages, carbonate linkages, amide linkages, oxymethyleneimine linkages, hydrazide linkages, silyl linkages, sulfide linkages, disulfide linkages, sulfone linkages, sulfoxide linkages, sulfonate linkages, sulfonamide linkages, formacetal linkages, thioformacetal linkages, oxime linkages and ethylene glycol linkages.

33. A macromolecule of claim 26 wherein said first nucleoside region includes at least two α-nucleoside linked by a charged or neutral 3′-5′ phosphorous linkages.

34. A macromolecule comprising a plurality of units linked by covalent linkages in a sequence that is hybridizable to a complementary nucleic acid, wherein:

said units are selected from nucleosides and nucleobases:

said nucleosides are selected from α-nucleosides, ß-nucleosides including 2′-deoxy-erythro-pentofuranosyl ß-nucleosides, 4′-thionucleosides, and carbocyclic-nucleosides;

said nucleobases are selected from purin-9-yl and pyrimidin-1-yl heterocyclic bases;

said linkages are selected from charged 3′-5′ phosphorous, neutral 3′-5′ phosphorous, charged 2′-5′ phosphorous, neutral 2′-5′ phosphorous or non-phosphorous linkages; and

said sequence of linked units is divided into at least two regions, wherein:

a first of said regions includes said nucleobases linked by non-phosphorous linkages and nucleobases that are attached to phosphate linkages via non-sugar tethering groups, and nucleosides selected from said α-nucleosides linked by charged and neutral 3′-5′ phosphorous linkages, said α-nucleosides linked by charged and neutral 2′-5′ phosphorous linkages, said α-nucleosides linked by non-phosphorous linkages, said 4′-thionucleosides linked by charged and neutral 3′-5′ phosphorous linkages, said 4′-thionucleosides

linked by charged and neutral 2′-5′ ph sphorous linkages, said 4′-thionucleosides linked by non-phosphorous linkages, said carbocyclic-nucleosides linked by charged and neutral 3′-5′ phosphorous linkages, said carbocyclic-nucleosides linked by charged and neutral 2′-5′ phosphorous linkages, said carbocyclic-nucleosides linked by non-phosphorous linkages, said ß-nucleosides linked by charged and neutral 2′-5′ linkages, and said ß-nucleosides link d by non-phosphorous linkages; and

a second of said regions includes said 2′-deoxy-erythro-pentofuranosyl ß-nucleosides linked by charged 3′-5′ phosphorous linkages having a negative charge at physiological pH.

35. The macromolecule of claim 34 wherein said first region includes at least two nucleobases linked by a non-phosphate linkage.

36. The macromolecule of claim 35 wherein said non-phosphate linkage is a peptide linkage.

37. The macromolecule of claim 35 wherein said second region is positioned between said first region and a third region, said third region including said nucleobases linked by non-phosphorous linkages and nucleobases that are attached to phosphate linkages via a non-sugar tethering moiety, and nucleosides selected from said α-nucleosides linked by charged and neutral 3′-5′ phosphorous linkages, said α-nucleosid s linked by charged and neutral 2′-5′ phosphorous linkages, said α-nucleosides linked by non-phosphorous linkages, said 4′-thionucleosides linked by charged and neutral 3′-5′ phosphorous linkages, said 4′-thionucleosides linked by charged and neutral 2′-5′ phosphorous linkages, said 4′-thionucleosides linked by non-phosphorous linkages, said carbocyclic-nucleosides link d by charged and neutral 3′-5′ phosphorous linkages, said carbocyclic-nucleosides linked by charged and neutral 2′-5′ phosphorous linkages, said carbocyclic-nucleosides linked by non-phosph rous linkages, said ß-nucleosides linked by charged and neutral 2′-5′ linkages, and said ß-nucleosides linked by

non-phosphorous linkages.

38. A macromolecule of claim 35 wherein said nucleobases are selected from adenine, guanine, cytosin , uracil, thymine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl adenine, 2-propyl and other alkyl adenine, 5-halo uracil and cytosine, 6-azo uracil, cytosine and thymine, 5-uracil (pseudo uracil), 4-thiouracil, 8-halo, amino, thiol, thiolalkyl, hydroxyl and other 8 substituted adenine and guanine, or 5-trifluoromethyl uracil and cytosine.

39. A macromolecule comprising a plurality of units linked by covalent linkages in a sequence that is hybridizable to a complementary nucleic acid, wherein:

said units are selected from nucleosides and nucleobases;

said nucleosides are selected from α-nucleosides, ß-nucleosides, 4′-thionucleosides and carbocyclic-nucleosides;

said nucleobases are selected from purin-9-yl and pyrimidin-1-yl heterocyclic bases;

said linkages are selected from charged phosphorous, neutral phosphorous or non-phosphorous linkages; and

said sequence of linked units is divided into at l ast two regions, wherein:

a first of said regions includes said α-nucleosides linked by charged and neutral 3′-5′ phosphorous linkages, said α-nucleosides linked by charged and neutral 2′-5′ phosphorous linkages, said α-nucleosides linked by non-phosphorous linkages, said 4′-thionucleosides linked by charged and neutral 3′-5′ phosphorous linkages, said 4′-thionucleosides linked by charged and neutral 2′-5′ phosphorous linkages, said 4′-thionucleosides linked by non-phosphorous linkages, said carbocyclic-nucleosides linked by charged and neutral phosphorous linkag s, said carbocyclic-nucleosides linked by non-phosphorous linkag s, said ß-nucl sid s linked by charged and n utral 3′-5′ linkages, said ß-nucleosides linked by charged and neutral 2′-5′

linkages, and said β-nucl osid s linked by non-phosphorous linkages; and

a second of said regions including said nucleobases linked by non-phosphorous linkages and nucleobases that are attached to phosphate linkages via a non-sugar tethering moiety.

40. The macromolecule of claim 38 wherein said non-phosphate linkage is a peptide linkage.

41. A macromolecule of claim 38 including a plurality of said first regions.

42. A macromolecule of claim 38 including a plurality of said second regions.

43. A macromolecule of claim 41 including a plurality of said first regions.

44. A method of treating an organism having a disease characterized by the undesired production of a protein comprising contacting the organism with a compound of claim 34.

45. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound of claim 34 and a pharmaceutically acceptable diluent or carrier.

46. A method of modifying *in vitro* a sequenc - specific nucleic acid, comprising contacting a test solution containing a RNase H and said nucleic acid with a compound f claim 34.

47. A method of treating an organism having a disease characterized by the undesired production of a protein comprising contacting the organism with a compound of claim 39.

48. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound of claim 39 and a pharmaceutically acceptable diluent or carrier.